NATIONAL MARROW DONOR PROGRAM®

Entrusted to operate the C.W. Bill Young Cell Transplantation Program,
including Be The Match Registry℠

November 04, 2009

Cdr. Elizabeth Montcalm-Smith
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: **Quarterly Performance/Technical Report of the National Marrow Donor Program®**

Reference: Grant Award #N00014-08-1-0058 between the Office of Naval Research and the National Marrow Donor Program

Dear Cdr. Montcalm-Smith:

Enclosed is subject document which provides the performance activity for each statement of work task item of the above reference for the period of August 1, 2009 to September 30, 2009.

Should you have any questions as to the scientific content of the tasks and the performance activity of this progress report, you may contact our Chief Medical Officer – Dennis L Confer, MD directly at 612-362-3425.

With this submittal of the quarterly progress report, the National Marrow Donor Program has satisfied the reporting requirements of the above reference for quarterly documentation. Other such quarterly documentation has been previously submitted under separate cover.

Please direct any questions pertaining to the cooperative agreement to my attention (612-362-3403 or at cabler@nmdp.org).

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, MA
Sr. Contracts Representative

Enclosure: Quarterly Report with SF298

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REPORT DOCUMENTATION PAGE

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14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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NATIONAL MARROW DONOR PROGRAM®

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QUARTERLY
PERFORMANCE / TECHNICAL REPORT
FOR
JULY 01, 2009 to SEPTEMBER 30, 2009
PERIOD 7

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
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QUARTER PROGRESS REPORT

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

July 01, 2009 through September 30, 2009

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IIA.1.2 Aim 2: GCSF in Radiation Exposure	**Period 7 Activity:** • No activity this period
IIA.1 3 Aim 3: Patient Assessment Guidelines and System Enhancements	**Period 7 Activity:** • No activity this period
IIA 1.4 Aim 4: National Data Collection Model	**Period 7 Activity:** • No activity this period
IIA. Contingency Preparedness – Hypothesis 2: Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.	
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IIA.2.2 Aim 2: Sibling Typing Standard Operating Procedures	**Period 7 Activity:** • No activity this period

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IIB. Rapid Identification of Matched Donors – Hypothesis 1: Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.	
IIB.1.1 Aim 1: Increase Registry Diversity	**Period 7 Activity:** Two abstracts detailing results of two allele frequency analysis projects were submitted to the American Society for Histocompatibility and Immunogenetics 2009 annual meeting. Both abstracts were accepted for poster presentations early next quarter. • African American adult volunteers with DRB1*1501 vs. 1503 • DRB1*0811 in Native American samples typed previously as DRB1*0802 or with codes that include DRB1*0802. Three retyping projects were completed this period. Results of these projects improved the HLA typing quality of listed adult donors and allows for improved speed of donor selection for patients with these alleles, including non-Caucasian patient searches. Specific alleles retested were: • The allele A*2423 was described in April 1999 and was thought to be relatively uncommon but seen in NAM populations. Until reagents were added to type for A*2423, samples would have been reported as A*2403 or with codes that contain the A*2403 allele. Twenty NAM samples were retyped and 70% of the donors' typings were corrected to reflect the new updated allele, A*2423.

	• The allele A*3010 was described in January 2001 and is seen most often in the conserved haplotype A*3010-B*4101-DRB1*0405. Until reagents were added to type for A*3010, samples would have been reported as A*3002. It was postulated that donors typed before 2002 with the haplotype A*3002-B*4101-DRB1*0405 may actually carry A*3010. 117 donors were retyped. 87% carried A*3010 rather than A*3002. 82% of the donors retyped were Hispanic. • DRB1*1506 retyping project on 221 Asian samples identified 32% of donors had discrepant types at A, B, or DRB1. Although DRB1*1506 was only found in 3% of the samples, 15.4% of the DRB1 typings were identified to be discrepant from previous results.
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IIB.1.3 Aim 3: Evaluate HLA-C Typing of Donors	**Period 7 Activity:** • This task is closed.
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IIB 2.3 Aim 3: Reinterpretation of Primary Data	**Period 7 Activity:** • This task is closed.
IIB 2.4 Aim 4: Genotype Lists & Matching Algorithm	**Period 7 Activity:** • No activity this period
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IIB 3.2 Aim 2: Enhancement of EM Algorithm	**Period 7 Activity:** • No activity this period
IIB 3.3 Aim 3: Optimal Registry Size Analysis	**Period 7 Activity:** • No activity this period

IIB 3.4 Aim 4: Target Under-represented Phenotypes	**Period 7 Activity:** • No activity this period
IIB 3.5 Aim 5: Bioinformatics Web Site	**Period 7 Activity:** • This task is closed.
IIB 3.6 Aim 6: Consultants to Improve Algorithm	**Period 7 Activity:** Funding on this aim provides support for the SSA program provided to TCs to meet their need for HLA expertise for unrelated stem cell donor selection. The program includes external and internal HLA experts who review each patient search and write a report summarizing a search strategy to assist the TC in rapidly identifying the best potential stem cell source for their patient. The HLA experts provided valuable feedback for algorithm and IT enhancements throughout the quarter. The SSA program completed 407 patient reports for 74 TCs during this quarter. The average turnaround time for all reviews was 3.6 business days which met the program requirement of 5 business days. • A one day in person meeting for all search strategy advisors/consultants was held at the NMDP Coordinating Center to discuss the latest search strategy review procedures and best practices, transplant center practices, HLA research topics, and future algorithm and system plans.
IIB. Rapid Identification of Matched Donors – Hypothesis 4: Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.	
IIB.4.1 Aim 1: Expand Network Communications	**Period 7 Activity:** • No activity this period
IIB.4.2 Aim 2: Central Contingency Management	**Period 7 Activity:** • No activity this period

IIB.4.3 Aim 2: Benchmarking Analysis	**Period 7 Activity:** • This task is closed.
IIB.4.4 Aim 2: Expand Capabilities of Collection and Apheresis Centers	**Period 7 Activity:** • No activity this period
IIC. Immunogenetic Studies – Hypothesis 1: HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations it will not be possible to delay transplant until a perfectly matched donor can be found.	
IIC.1.1 Aim 1: Donor Recipient Pair Project	**Period 7 Activity:** In 1994 a retrospective D/R Pair HLA typing project to characterize class I and class II alleles of donor/recipient paired samples from NMDP's Repository was initiated. The goals of this ongoing research project are to assay the impact of DNA-based HLA matching on unrelated donor transplant outcome, develop strategies for optimal HLA matching, evaluate the impact of matching at alternative HLA loci on transplant outcome and finally to promote the development of DNA-based high resolution HLA typing methodologies. • All outstanding typing issues from prior SGs were compiled and assigned to a Tie-Breaker lab. Full analysis and audit will be completed early next quarter. • 273 pairs of sample Group 22 whose period of performance came to a close on April 30, 2009 have been audited and are available for inclusion in research studies. • The project period for SG23 came to a close on August 31, 2009. The contracts for SG23 (400 pairs) testing include intermediate and high resolution HLA. No-Make resolution and discrepancy analysis have been initiated. Audit of the 400 pairs will occur next quarter. • Sample Group 24 (400pairs) was initiated on August 31, 2009. Inclusion of high resolution DPB1 typing on all samples occurred within SG 24. The period of performance is from August 31, 2009 to December 31, 2009.

	Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the ARS. This recommendation is based on the hypothesis that amino acid differences outside the ARS are not immunogenic. The ARS allo-reactivity assessment project will give insight into the allowable percent tolerance of matching needed outside of the ARS. • Initiated investigation of the first class II non-ARS mismatch (DRB1*140101/1454) where both alleles have been seen in the same genotype. Specific queries of the Be The Match Registry allowed for selection of ninety-nine potential donors to be typed at high resolution. • HLA-A, B, C, DRB1/3/4/5, DQA/B1 and DPB1 typings were completed on all 99 donors. Selection of potential study participants is ongoing.
IIC. Immunogenetic Studies – Hypothesis 2: Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.	
IIC 2.1 Aim 1: Analysis of non-HLA loci	**Period 7 Activity:** In 2005 a pilot study to perform high resolution KIR gene typing was launched. The primary objectives of the study were to move technology forward from the current practice of locus level typing to high resolution typing, disseminate information and protocols in an open source mechanism and develop reference lines for use in individual laboratories. • Resolution continued on 128 potential new KIR alleles found within Phase 1, 2 and 3 of the KIR Typing Pilot. 78 samples were determined to have 48 novel alleles. Submission, naming and publication should occur within the next two quarters. • Manuscript preparation for the KIR Typing Pilot Project continued. Haplotype and L.D. predictions were completed. The data, including allele frequencies and haplotype/L.D. predictions were presented at the KIR 2009 Polymorphism Workshop. Also, availability of samples and data to external researchers was promoted. • To date 1500 pairs from the Donor/Recipient pair's project have been typed for presence/absence of 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1).

	• Comparison analysis of the KIR presence/absence typing on samples from SG 21-23 has been completed. • 60 reference cell lines were selected for expansion. 58 lines succeeded and expansion is in progress.
IIC 2.2 Aim 2: Related Pairs Research Repository	**Period 7 Activity:** Related transplant research sample collection continued with a pilot project initiated at seven TCs in December 2007. By the end of the reporting period, five TCs had submitted 677 samples (317 donor/recipient pairs) to the Repository. • Development continues on the Research Sample Repository Tools suite to facilitate management of samples. Several enhancements were tested and released to production. • Reports to improve sample submission tracking and to better understand the reasons for non-submission are being designed. Reports will be coupled to Continuous Process Improvement Phase III. Reports should be available starting next quarter. • Sample collection will be expanded to additional BMT-CTN core centers following successful updates to the sample tracking software. • The Whole Genome Amplification project will continue with large scale WGA implementation for low quantity sample expansion. .
IID. Clinical Research in Transplantation – Hypothesis 1: Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.	
IID.1.1 Aim 1: Observational Research, Clinical Trials and NIH Transplant Center	**Period 7 Activity:** The Cord Blood Research sub-Committee met monthly to discuss study priorities and plan analyses. Activity during the past quarter focused on the following areas: • The challenge grant application to the NHLBI to support a study to investigate biomarkers associated with cord blood engraftment was not awarded. The study protocol was re-evaluated and revised to allow the study to proceed with ONR support.

	○ The Duke laboratory conducted an on-site training session with the MD Anderson laboratory staff to standardize testing methodologies for the assay validation phase of the project. • Work continued on the observational study of single versus double cord blood transplants in adults. Preliminary data analysis has been completed, but is not ready for dissemination. • Two cord blood workshops have been organized for the 2009 NMDP Council Meeting. ○ Cord Blood Transplants in Adults: A Growing Therapy: Session objectives are to review history of cord blood transplantation in adult patients, to discuss current practices in adult cord blood transplants, and to describe the role of cord blood in the future of adult stem cell transplantation. ○ Strategies for Improving Outcomes in Cord Blood Transplant: Research and Practice: Session objectives are to review historical outcome data for cord blood transplant, to discuss the limitations of cord blood transplants, and to discuss innovation techniques that focus on improving cord blood transplant. • The study design for a post thaw assessment of cord blood viability was submitted for consideration to the Research Subcommittee by PIs Allison Hubel and David McKenna. The committee determined that existing data from a study performed by a subcommittee member obviates the need to repeat the study as proposed. • Work continued on the development of a white paper detailing recommendations/guidelines for the assessment of new assays (potency or other assays) relevant to cord blood banking and/or transplantation. A draft version of the paper is to be completed for review at the Cord Committee Meeting in the next quarter.
IID.1.2 Aim 2: Research with NMDP Donors	**Period 7 Activity:** • No activity this period

IID.1.3 Aim 3: Expand Immuno-biology Research	**Period 7 Activity:** The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies • The scientific director and Ph.D. statisticians attended and participated in the CIBMTR External Scientific Agenda review. • Five manuscripts were submitted for publication: o David Valcarcel, et al. *One Antigen Mismatched Related vs. HLA-Matched Unrelated Donor Hematopoietic Transplantation in Adults with Acute Leukemia: CIBMTR Results in the Era of Molecular Typing.* Submitted to Blood. o Stephen Spellman, et al. *The Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Hematopoietic Cell Transplantation is Predictive of Graft Failure.* Submitted to Blood. o Susana Marino, et al. *Mismatched Unrelated Donor Stem Cell Transplantation: Identification of HLA Class I Amino Acid Substitutions Associated with Survival at Day 100*. Submitted to Blood. o David McDermott, et al. *Donor and Recipient Chemokine Receptor CCR5 Genotype is Associated with Survival after Bone Marrow Transplantation.* Submitted to Blood. o Yume Nguyen, et al. *Insufficient Evidence for Association of NOD2/CARD15 or Other Inflammatory Bowel Disease-Associated Markers on GVHD Incidence or Other Adverse Outcomes in T-Replete, Unrelated Donor Transplantation.* Submitted to Blood. • Two abstracts were submitted and accepted for presentation at the 2009 American Society of Hematology annual meeting: o Yasuo Morishima, et al. *Impact of Donor-Recipient Ethnicity on Risk of Acute Graft-Versus-Host Disease, Leukemia Relapse and Survival in Hematopoietic Stem Cell Transplantation from HLA-Compatible Unrelated Donors. A Report from the International Histocompatibility Workshop Group.* Accepted for oral presentation. o Sarah Cooley, et al. *Choosing Donors with Favorable KIR B Genotypes for Unrelated Hematopoietic Transplantation Results in Superior Relapse Protection and Better Relapse-Free Survival for Patients with AML.* Accepted for oral presentation.

	Funding for CIBMTR IBWC studies: • Research funds were awarded to support DNA extraction and preparation of 408 samples for a study evaluating genome wide genetic diversity and the impact on acute graft versus host disease. The extractions will be completed early next quarter.

ACRONYM LIST

AABB	American Association of Blood Banks	ICRHER	International Consortium for Research on Health Effects of Radiation
AGNIS	A Growable Network Information System	IS	Information Services
AML	Acute Myelogenous Leukemia	IT	Information Technology
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)	IRB	Institutional Review Board
ASBMT	American Society for Blood and Marrow Transplantation	JCAHO	Joint Commission on Accreditation of Healthcare Organizations
ASHI	American Society for Histocompatibility and Immunogenetics	KIR	Killer Immunoglobulin-like Receptor
B-LCLs	B-Lymphoblastoid Cell Lines	NCI	National Cancer Institute
BARDA	Biomedical Advanced Research and Development Authority	MHC	Major Histocompatibility Complex
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network	MICA	MHC Class I-Like Molecule, Chain A
BRT	Basic Radiation Training	MICB	MHC Class I-Like Molecule, Chain B
C&A	Certification and Accreditation	MDACC	MD Anderson Cancer Center
CBMTG	Canadian Blood and Marrow Transplant Group	MSKCC	Memorial Sloan-Kettering Cancer Center
CBB	Cord Blood Bank	MUD	Matched Unrelated Donor
CBC	Congressional Black Caucus	NEMO	
CBS	Canadian Blood Service	NCBM	National Conference of Black Mayors
CBU	Cord Blood Unit	NHLBI	National Heart Lung and Blood Institute
CHTC	Certified Hematopoeitic Transplant Coordinator	NIH	National Institutes of Health
CIBMTR	Center for International Blood & Marrow Transplant Research	NIMS	National Incident Management System
CLIA	Clinical Laboratory Improvement Amendment	NK	Natural Killer
CME	Continuing Medical Education	NMDP	National Marrow Donor Program
CMF	Community Matching Funds	NRP	National Response Plan
COG	Children's Oncology Group	NST	Non-myeloablative Allogeneic Stem Cell Transplantation

CREG	Cross Reactive Groups	OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
CSS	Center Support Services	OIT	Office of Information Technology
CT	Confirmatory Testing	OMB	Office of Management and Budget
CTA	Clinical Trial Application	ONR	Office of Naval Research
DC	Donor Center	P2P	Peer-to-Peer
DIY	Do it yourself	PBMC	Peripheral Blood Mononuclear Cells
DKMS	Deutsche Knochenmarkspenderdatei	PBSC	Peripheral Blood Stem Cell
DMSO	Dimethylsulphoxide	PCR	Polymerase Chain Reaction
DNA	Deoxyribonucleic Acid	PSA	Public Service Announcement
D/R	Donor/Recipient	QC	Quality control
EBMT	European Group for Blood and Marrow Transplantation	RCC	Renal Cell Carcinoma
EM	Expectation Maximization	RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
EMDIS	European Marrow Donor Information System	REAC/TS	Radiation Emergency Assistance Center/Training Site
ERSI	Environment Remote Sensing Institute	RFP	Request for Proposal
FBI	Federal Bureau of Investigation	RFQ	Request for Quotation
FDA	Food and Drug Administration	RG	Recruitment Group
FDR	Fund Drive Request	RITN	Radiation Injury Treatment Network
Fst	Fixation Index	SBT	Sequence Based Typing
GETS	Government Emergency Telecommunications Service	SCTOD	Stem Cell Therapeutics Outcome Database
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)	SG	Sample Group
GIS	Geographic Information System	SLW	STAR Link® Web
GvHD	Graft vs Host Disease	SSA	Search Strategy Advice
HCT	Hematopoietic Cell Transplantation	SSO	Sequence Specific Oligonucleotides
HHS	Health and Human Services	SSP	Sequence Specific Primers
HIPAA	Health Insurance Portability and Accountability Act	SSOP	Sequence Specific Oligonucleotide Probes

HLA	Human Leukocyte Antigen	STAR®	Search, Tracking and Registry
HML	Histoimmunogenetics Mark-up Language	TC	Transplant Center
HR	High Resolution	TED	Transplant Essential Data
HRSA	Health Resources and Services Administration	TNC	Total Nucleated Cell
HSC	Hematopoietic Stem Cell	TSA	Transportation Security Agency
IBWC	Immunobiology Working Committee	UI	User Interface
IDM	Infectious Disease Markers	URD	Unrelated Donor
IHWG	International Histocompatibility Working Group	WGA	Whole Genome Amplification
IPR	Immunobiology Project Results	WMDA	World Marrow Donor Association
IND	Investigational New Drug	WU	Work-up